Treatment strategies for postviral olfactory dysfunction: A systematic review

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ABSTRACT

Background: *The coronavirus disease 2019 (COVID-19) pandemic has been associated with a dramatic increase in postviral olfactory dysfunction (PVOD) among patients who are infected. A contemporary evidence-based review of current treatment options for PVOD is both timely and relevant to improve patient care.*

Objective: *This review seeks to impact patient care by qualitatively reviewing available evidence in support of medical and procedural treatment options for PVOD. Systematic evaluation of data quality and of the level of evidence was completed to generate current treatment recommendations.*

Methods: *A systematic review was conducted to identify primary studies that evaluated treatment outcomes for PVOD. A number of medical literature data bases were queried from January 1998 to May 2020, with completion of subsequent reference searches of retrieved articles to identify all relevant studies. Validated tools for the assessment of bias among both interventional and observational studies were used to complete quality assessment. The summary level of evidence and associated outcomes were used to generate treatment recommendations.*

Results: *Twenty-two publications were identified for qualitative review. Outcomes of alpha-lipoic acid, intranasal and systemic corticosteroids, minocycline, zinc sulfate, vitamin A, sodium citrate, caroverine, intranasal insulin, theophylline, and* Gingko biloba *are reported. In addition, outcomes of traditional Chinese acupuncture and olfactory training are reviewed.*

Conclusion: *Several medical and procedural treatments may expedite the return of olfactory function after PVOD. Current evidence supports olfactory training as a first-line intervention. Additional study is required to define specific treatment recommendations and expected outcomes for PVOD in the setting of COVID-19.*

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The alteration or loss of the sense of smell affects roughly 12.4% of adults > 40 years old, with an estimated annual prevalence of 13.3 million in the United States.[1,2] Olfactory dysfunction (OD) may arise from disparate mechanisms, broadly categorized as sensorineural (including head trauma, neurodegenerative disorders, chemical injury), conductive (chronic sinusitis with nasal polyps, central compartment airway disease), or mixed. Sensorineural OD may also occur as a sequela of a viral upper respiratory tract infection (URTI), termed postviral OD (PVOD). The ongoing coronavirus disease 2019 (COVID-19) pandemic has drawn attention to PVOD, which affects > 50% of patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[3] In a meta-analysis of COVID-19 associated OD by Hannum *et al.*,[4] the investigators used a random-effects model and computed an overall prevalence estimate of 50.2% (95% CI, 38.9–61.5%). Before the emergence of SARS-CoV-2, 18 to 42% of patients with OD were associated with a preceding viral upper respiratory infection.[5] It is currently unknown to what extent COVID-19–associated PVOD mechanistically mimics or differs from PVOD associated with other known viruses. However, COVID-19 is recognized to more frequently and distinctly induce OD compared with other viral infections, with incomplete recovery of smell, and that affected up to two-thirds of patients.[6] As the impact of COVID-19 continues to rise, we anticipate exponential growth in the numbers of patients seeking care for PVOD.[7]

Objective assessment of OD generally involves testing three components of olfaction, odor threshold,

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odor discrimination, and odor identification to yield a composite score, which has demonstrated greater sensitivity for the detection of OD compared with individual component scores.[8] Several validated tests are available to assess single or multiple components of olfaction in clinical and research environments, and are described in a contemporary review of OD assessment.[9] Self-reported quantitate olfactory changes have recently been validated for the clinical diagnosis of COVID-19 [10,11]

OD significantly impacts quality of life and has been associated with depression and an increased risk of future mortality.[12–14] Patients often report diminished enjoyment of food and concerns with regard to the inability to detect environmental hazards such as gas, smoke, or spoiled food.[15] A major public health concern, the inability to detect warning odors of smoke and of natural gas in adults > 70 years old, has been reported to be 20.3% and 31.3%, respectively.[16] Patients who experience OD are two to three times more likely to experience a hazardous event compared with their normosmic counterparts.[2] Several medical and procedural interventions have been evaluated to treat PVOD, with significant variability in study design and the associated level of evidence (LOE). This article systematically reviews the evidence related to medical and procedural interventions for PVOD to provide an initial framework for clinicians who treat PVOD that results from COVID-19.

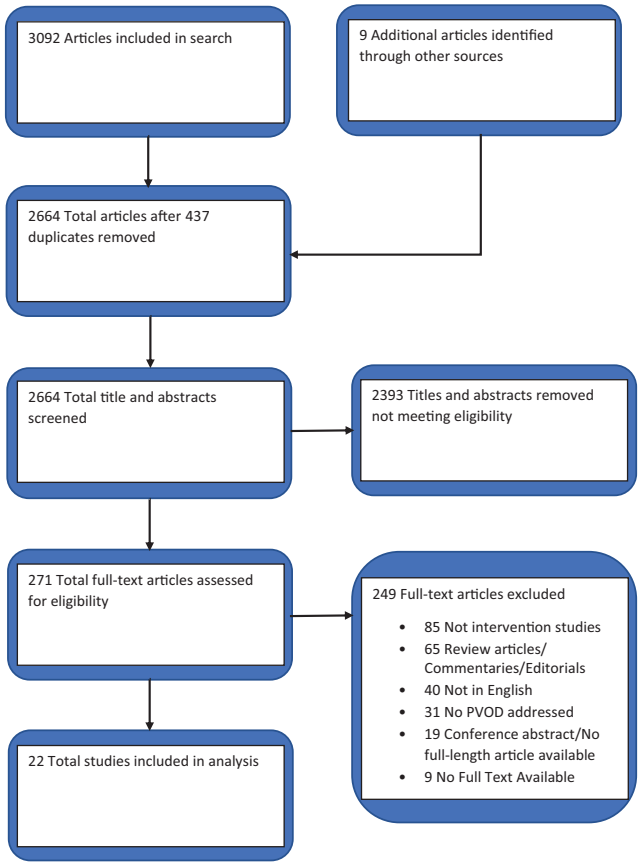

Figure 1. *PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.*

METHODS

This study has been prospectively indexed in the PROSPERO (International Prospective Register of Systematic Reviews), no. 202322.[17] The PRISMA (Preferred Reprting Items for Systematic Reviews and Meta-Analyses) guidelines[18] were used to identify and qualitatively analyze current evidence in support of treatment options for PVOD (Fig. 1).[18] MEDLINE (National Library of Medicine, Bethesda, Maryland)/PubMed and Embase (Elsevior, Amsterdam, Netherlands) data bases were queried with the following terms to complete a systematic review: anosmia, hyposmia, postinfectious, virus, and URTI. A complete search strategy for each data base is provided in Supplemental Table 3. Two authors (J.A. and S.B.) independently reviewed the titles and abstracts of all identified citations. Primary literature that evaluated the safety and efficacy of treatment outcomes for PVOD were included. Exclusion criteria were the following: reviews, commentaries, editorials, nonhuman studies, anosmia from nonviral etiologies, non-English articles, and studies in which nested analysis of the subjects with postviral etiology was not possible. A bibliographic review of the included studies was also completed to identify manuscripts not found in our search strategy.

S.N. Helman and J. Adler are co–first authors. Author contributions included the following. S.N. Helman, A. Jafari, and J.M. Levy made substantial contributions to the conception and design, acquisition of data, analysis and interpretation of data, and drafted and reviewed the article critically for important intellectual content. J. Adler made substantial contributions to the acquisition of data, and drafted and reviewed the article critically for important intellectual content. J.R. Vuncannon made substantial contributions to the acquisition of data, and analysis and interpretation of data, and drafted and reviewed the article critically for important intellectual content. S. Bennet and A.C. Cozart made substantial contributions to the acquisition of data and reviewed the article critically for important intellectual content. S.K. Wise and M.E. Kuravilla made substantial contributions to the conception and design, and analysis and interpretation of data, and reviewed the article critically for important intellectual content. All the authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work related to its accuracy or integrity.

After identification of the included studies, formatted summary tables were used to complete primary data extraction. Two senior authors (S.H. and J.L.) independently verified data extraction and resolved inconsistencies. The following information was extracted: author

(s), year, LOE and study design, demographics of the patient sample, extent of OD, method to confirm OD, medical or procedural intervention, and treatment outcomes. According to the recommendations of Zeng *et al.*,[19] the following tools were used to assess risk of bias: Cochrane Collaboration's Tool (Cochrane, London, United Kingdom) for randomized controlled trials (RCT) (Table 1).[20] The Methodological Index for Non-Randomized Studies scale for nonrandomized interventional studies[21] (Table 2) and the Newcastle-Ottawa Scale for nonrandomized observational studies (Table 3).[22] Results were collated for qualitative and quantitative analysis. Studies were graded from 1 to 5 by using the Oxford LOE.[23] Treatment recommendations were examined and defined on their aggregate grade of evidence by using established guidelines.[24]

RESULTS

Twenty-two studies were identified for qualitative review.[25–46] The component LOE included nine 1B studies, four 1C, eight 2B, and one 3B study. Data from a total of 1325 subjects were obtained. Among the 909 subjects with the sex reported, 67% (n = 612) were women. The mean ± standard deviation (SD) age was 55.86 ± 9.60 years among 682 subjects with reported age reported. The risk of bias analyses for RCT, non-RCT, and observational studies are reported in the Tables 1–3. Due to heterogeneity in study design, treatments, and outcome measures, a meta-analysis with a calculation of effect sizes could not be completed.

Medical Therapies for the Treatment of PVOD

Thirteen studies that evaluated the efficacy of medical therapies for the treatment of PVOD were identified for review.[25–37] A summary of the included studies is found in Supplemental Table 1, with data from 798 subjects. Among subjects with the sex reported, 71% (n = 310) were women. The mean ± SD age reported was 54.80 ± 6.51 years (n = 211).

Alpha-Lipoic Acid. Alpha-lipoic acid, used to treat diabetic neuropathy, acts as an antioxidant and stimulator

Table 1 **Results of Cochrane's Collaboration tool for assessing risk of bias in randomized controlled trials**

Study	Selection Bias		Performance Bias: Blinding of Participants and Personnel	Detection Bias: Blinding of Outcome Assessment	Attrition Bias: Incomplete Outcome Data	Reporting Bias: Selecting Reporting	Total: Low on Risk of Bias
	Random Sequence Generation	Allocation Concealment					
Reden *et al.*,[28] 2011	Unclear	Low risk	Low risk	Low risk	Low risk	Unclear	4/6
Reden *et al.*,[30] 2012	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	5/6
Quint *et al.*,[32] 2002	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear	1/6
Dai *et al.*,[38] 2016	Low risk	High risk	High risk	Unclear	Low risk	Unclear	2/6
Damm *et al.*,[40] 2014	Low risk	Unclear	High risk	Low risk	Low risk	Unclear	3/6
Seo *et al.*,[27] 2009	Low risk	Unclear	Unclear	Unclear	Low risk	Unclear	2/6
Whitcroft *et al.*,[33] 2016	Low risk	Low risk	High risk	Unclear	Low risk	Unclear	3/6
Philpott *et al.*,[34] 2017	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	5/6
Whitcroft *et al.*,[35] 2017	High risk	Unclear	High risk	Unclear	Low risk	Low risk	2/6
Patel *et al.*,[41] 2017	Low risk	Unclear	High risk	High risk	High risk	Low risk	2/6
Schopf *et al.*,[37] 2015	High risk	Unclear	High risk	High risk	Low risk	Low risk	2/6

Table 2 **Results of Methodological Index for Non-randomized Studies tool for assessing risk of bias in nonrandomized interventional studies**

Methodological Items for Nonrandomized Studies	Konstantinidis *et al.*,[43] 2016	Kollndorfer *et al.*,[46] 2015	Vent *et al.*,[39] 2010	Henkin *et al.*,[36] 2009	Hummel *et al.*,[31] 2017	Fornazieri *et al.*,[45] 2020	Qiao *et al.*,[44] 2019	Fukazawa *et al.*,[26] 2005	Geissler *et al.*,[42] 2014	Hummel *et al.*,[25] 2002
1. Clearly stated aim	2	2	2	2	2	2	2	2	2	2
2. Inclusion of consecutive patients	1	1	2	2	2	2	2	2	2	2
3. Prospective collection of data	2	0	0	0	0	0	0	0	2	2
4. End points appropriate to study aim	1	2	2	2	2	2	2	2	2	2
5. Unbiased assessment of study endpoint	0	1	0	1	0	0	0	0	0	1
6. Follow-up period appropriate to aim	2	2	2	2	2	2	2	0	2	2
7. Loss to follow up < 5%	2	1	2	2	2	1	1	2	2	2
8. Prospective calculation of study size included if comparative study (9–12):	0	0	0	0	0	0	0	0	0	0
9. Adequate control group	2	2	1	1	2	NA	NA	NA	NA	NA
10. Contemporary groups	2	2	1	1	2	NA	NA	NA	NA	NA
11. Baseline equivalence of groups	2	0	2	2	2	NA	NA	NA	NA	NA
12. Adequate statistical analyses	2	2	1	2	2	NA	NA	NA	NA	NA
Total	16/24	15/24	15/24	17/24	18/24	9/16	9/16	8/16	12/16	13/16

NA = Not applicable.
Items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). Items 9-12 apply only for comparative studies. The ideal score is 16 for noncomparative studies and 24 for comparative studies.

Table 3 **Results of Newcastle Ottawa scale for assessing the risk of bias in a nonrandomized observational study**

Study	Selection				Comparability	Outcomes			Total
	Representativeness of Exposed Cohort	Selection of Nonexposed Cohort	Ascertainment of Exposure	Outcome Not Present at the Start of the Study		Assessment of Outcomes	Length of Follow-up of Cohorts	Adequacy of Follow-up of Cohorts	
Aiba et al.,[29] 1998	1	1	1	1	0	0	1	1	6/9

of nerve growth factor, substance P, and neuropeptide Y.[47,48] Hummel *et al.*[25] evaluated the efficacy of alpha-lipoic acid for the treatment of PVOD. Benefits were seen in objective threshold-discrimination-identification (TDI) scores ($p = 0.002$) and odor discrimination ($p = 0.005$).

Intranasal and Systemic Corticosteroids. Corticosteroids have been used for the treatment of OD in the setting of chronic rhinosinusitis (CRS). Most olfactory loss is the result of an insult from inflammatory milieu produced by disparate stimuli, including CRS or virally mediated acute rhinosinusitis and/or URTI. Research in animal models suggest that benefits may arise *via* reduction of inflammatory mediators and modulation of olfactory gene expression.[49] By using a corticosteroid injection in the region of the olfactory cleft, Fukazawa[26] found an improvement rate that approximated 50%. Seo *et al.*[27] found improvements in odor threshold and identification in patients treated with topical mometasone and oral prednisolone ($p < 0.001$) with or without the addition of *Ginkgo biloba.* In addition to the aforementioned studies that examined the utility of corticosteroids with specific attention to PVOD, a number of studies evaluated the efficacy of systemic and topical corticosteroids in the treatment of olfactory loss of various etiologies.[50–52] These studies include subjects with PVOD but do not include results of subjects after virus separate from subjects without virus, and were thus excluded.

Minocycline. Due to its anti-apoptotic properties, previous use as a neuroprotective therapy in neurologic disease, and benefit in mouse models of anosmia, minocycline has been evaluated for PVOD intervention.[53] However, no significant difference in the objective TDI score was demonstrated beyond placebo.[28]

Zinc Sulfate. Thought to treat gustatory disorders by regenerating taste receptors, the effects of zinc supplementation have been investigated in patients with PVOD but did not improve the rate of subjective symptom improvement compared with topical corticosteroids.[29]

Retinoic Acid. Retinoic acid plays a key role in the neurogenesis of olfactory neuroepithelium.[54] This agent has been studied for use in PVOD with conflicting data. In comparison with placebo, supplementation with 10,000 IU vitamin A demonstrated no benefit.[30] However, administration of 10,000 IU of topical vitamin A in conjunction with olfactory training (OT) demonstrated significant clinical improvement relative to OT alone ($p = 0.03$).[31]

Other Medical Therapies for the Treatment of PVOD

Several other medical therapies have been investigated for treatment efficacy of PVOD as monotherapy or an adjunct to other therapies.

G. biloba. G. biloba has shown enhanced olfactory neurogenesis in murine models.[55] Investigation of *G. biloba* as an adjunct to combination systemic and topical corticosteroids for PVOD found no statistically significant benefit when adding *G. biloba.*[27]

Caroverine. Caroverine, an N-methyl-D-aspartate antagonist, was theorized to have benefits for the treatment of PVOD by preventing glutamatergic neurotoxicity. This agent improved odor thresholds in patients who were anosmic ($p = 0.005$) and odor identification in both patients with anosmic and patients with hyposmic PVOD ($p = 0.042$) compared with zinc sulfate.[32]

Sodium Citrate. Sodium citrate is postulated to improve olfaction *via* calcium sequestration and subsequent depression of feedback inhibition in olfactory signal transduction. Evaluation of intranasal sodium citrate found significant improvement in identification scores among a PVOD cohort in subgroup analysis ($p = 0.02$), despite equivocal results for OD of all causes.[33] Intranasal sodium citrate has also demonstrated significant improvement in detection for most odors ($p < 0.05$) relative to intranasal sterile water[34] but not to saline solution.[35]

Theophylline. Oral administration of the phosphodiesterase inhibitor theophylline has demonstrated improvements in olfaction. Mechanistically, this may result from increasing cyclic adenosine monophosphate and cyclic guanosine monophosphate in nasal secretions, which are lower in individuals with hyposmia.[56] When oral theophylline was administered at varying doses, greater improvement was seen with higher doses, and improvement persisted while treatment continued.[36]

Topical Intranasal Insulin. Topical intranasal insulin has also been investigated and demonstrated improved odor thresholds in 60% of patients, with smaller improvements in odor discrimination. Odors were perceived significantly more intensely after insulin compared with placebo administration ($p = 0.043$), whereas hedonic ratings did not change significantly.[37]

Procedural Therapies for the Treatment of PVOD

Nine studies that evaluated the efficacy of procedural therapies for the treatment of PVOD were identified.[38–46] A summary of included studies that evaluated the efficacy of these interventions is found in Supplemental Table 2.

Traditional Chinese Acupuncture. Two studies were identified for review.[38,39] Data from a total of 80 subjects were obtained with a mean ± SD age of 55.64 ± 12.28 years; 60% of the included subjects were women (n = 48). Traditional Chinese acupuncture (TCA) has been used as a healing technique in China for almost 2000 years. Dai *et al.*[38] examined the effects of 3 months of TCA in 50 patients with OD refractory to standardized corticosteroid and OT therapy. Objective Smell Identification Test scores improved significantly in the TCA group compared with control at completion of therapy (Pearson $\chi^2 = 0.031$).Vent *et al.*[39] evaluated the impact of a course of 10 weekly, 30-minute TCA sessions in patients with persistent PVOD and found improved olfaction in the TCA group relative to the vitamin B supplementation control group ($p = 0.02$).

OT. Seven studies were identified for review.[40–46] Data from a total of 447 subjects were obtained. Among 391 subjects with the sex reported, 65% were women (n = 254). The mean ± SD age reported was 56.47 ± 10.33 years. Mammalian olfactory epithelium contains neural stem cells that undergo lifelong neurogenesis and enable neural plasticity to allow functional recovery from neurotoxic insults.[57,58] OT seeks to leverage these characteristics to improve olfaction by regularly stimulating olfactory neurons with a range of odorants (eucalyptus, lemon, rose, and cloves) in a structured fashion for defined periods of time (Supplemental Appendix 1). Notably, a 2016 meta-analysis of OT found benefit in the total TDI scores as well as odor identification and discrimination.[59] Further, functional magnetic resonance imaging (MRI) studies demonstrated alterations in connectivity among cortical olfactory networks after OT.[60] With regard to PVOD, three level-1 and four level-2 studies investigated the utility of OT to improve olfaction.[40–46]

Hummel *et al.*[61] first investigated this therapy in 2009 among patients with all-cause OD and found significant improvement in objective measures of olfaction compared with controls. Since that time, additional studies demonstrated added benefit with higher odorant concentrations and training durations beyond 16 weeks.[40,41] Damm *et al.*[40] performed a randomized, single-blind, multicenter, crossover study in subjects with PVOD that compared OT with high concentration odorants with low concentration odorants and found improvement in TDI scores at twice the rate of expected spontaneous recovery in the high-concentration odorant group; however, no statistically significant difference in recovery rates were seen among the high-concentration (25.7%) and low-concentration (14.9%) groups. A later study that used patient-sourced essential oil, and thus random concentrations of odorants, found 32% of patients with OT demonstrated > 10% improvement on the University of Pennsylvania Smell Identification Test (UPSIT) (Sensonics International, Haddon Heights, New Jersey) compared with 13% of controls.[41]

The optimum duration of therapy was investigated in multiple studies. Geißler *et al.*[42] demonstrated a

nonsignificant trend of improvement in TDI scores at 16 weeks but significant improvement at 32 weeks of treatment ($p = 0.021$). Konstantinidis *et al.*[43] compared outcomes among patients with PVOD by using a 16-week OT regimen, a 56-week OT regimen, or no OT, and found significant improvement in the mean TDI scores compared with controls in both intervention arms at 16 weeks ($p < 0.05$) with durable improvement in the 16-week training arm at the end of the follow-up period. Qiao *et al.*[44] found mean ± SD TDI scores at 3 months (20.53 ± 3.01; $p < 0.05$) and 6 months (22.48 ± 3.73; $p < 0.05$) of training were significantly higher compared with baseline (16.82 ± 2.67). Most recently, Fornazieri *et al.*[45] found improvement in the UPSIT scores among patients with PVOD in 33.3% of patients after 3 months of OT and in 40% after 6 months. Kollndorfer *et al.*[46] found significant improvement in odor detection thresholds ($p = 0.028$) when using a 12-week training regimen but no improvement in odor discrimination and identification. These investigators also used functional MRI to demonstrate that patients who were anosmic retained activity in the neural networks responsible for odorant detection despite an inability to consciously identify odors.[46]

Treatment Recommendations

Twelve medical and two procedural interventions were studied for the management of PVOD.[25–46] A summary assessment of each intervention with associated treatment recommendations are presented in Table 4. For a patient who presented with new onset, suspected PVOD, current data support the use of OT as a first-line intervention. Treatments such as topical steroids, sodium citrate, vitamin A, theophylline, and TCA may be considered an option in carefully selected patients. The available evidence does not support the use of systemic corticosteroids nor zinc sulfate for the treatment of PVOD. Due to a lack of rigorous study, no recommendation can be made for alpha-lipoic acid, caroverine, *G. biloba,* insulin, minocycline, theophylline, and vitamin B.

DISCUSSION

This systematic review identified two therapies that may be considered as first-line therapeutic options for PVOD to include OT and topical intranasal corticosteroids. Our recommendations consider the inflammatory insults mitigated by viral entry into olfactory structures. Briefly, neuroinvasion and neurotropism are putative mechanisms for cell injury, whereby SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) receptors, and enters the cell.[62] ACE2 receptors are found on olfactory epithelium and the structures that support olfactory neurons.[63] It is through this inflammatory mechanism that SARS-CoV-2 leads to altered taste, smell, and chemesthesis.[64]

OT shows promise in several prospective trials. Among all therapies for PVOD, OT has the largest LOE.[40-46] This, combined with a relatively low cost and absence of associated complications, supports its use as first-line therapy in adults with PVOD. Although the optimal OT training regimen has yet to be defined, the current evidence base supports a regimen that uses high-concentration odorants and a training length of ≥16 weeks for optimal outcomes.[40–46] Although TCA was found to be beneficial in two studies,[38,39] it is noted that the findings reported by Vent *et al.*[39] are contested in a letter to the editor.[65]

Table 4 **Medical and procedural treatments and associated recommendations**

Therapy	Level of Evidence Summary[23]	Recommendation
Medical Regimen		
Alpha-lipoic acid	C	No recommendation
Caroverine	B	No recommendation
Corticosteroids (systemic)	B	Recommend against
Corticosteroids (topical)	B	Option
Ginkgo biloba	C	No recommendation
Topical insulin	C	No recommendation
Minocycline	B	No recommendation
Sodium citrate (topical)	B	Option
Theophylline (topical)	C	No recommendation
Vitamin A	B	Option
Vitamin B	C	No recommendation
Zinc sulfate	B	Recommend against
Procedural regimen		
Olfactory training	B	Strongly recommend
Traditional Chinese acupuncture	B	Option

Several medical therapies have been evaluated for the treatment of PVOD with varied results as summarized in a previous systematic review of pharmacotherapies for PVOD. Here, caroverine and alpha-lipoic acid, along with systemic and topical corticosteroids, were seen as possible beneficial interventions, whereas minocycline, vitamin A, zinc sulfate, and *G. biloba* were deemed not beneficial.[66] Despite possible benefits of these pharmacotherapies, it must be noted that a recent position paper on OD highlights the absence of high-level evidence to support any pharmacologic treatment in the management of OD unrelated to CRS.[67]

Although acknowledging that further study is needed, we believe that the presented benefits of topical corticosteroid administration and the concomitant low risk of adverse effects support the use of topical corticosteroid as an option for first-line therapy. It remains unclear if viral illnesses lead to residual inflammation that can be targeted by steroids; however, COVID-19–induced PVOD has been anecdotally linked with inflammation of olfactory cleft as well as MRI evidence of viral invasion of olfactory bulb.[68,69] We contend that steroids may augment olfactory retraining by reducing mucosal inflammation and obstruction of the olfactory cleft.

Administration of topical steroids with irrigations may increase delivery of medication to the olfactory cleft compared with standard nasal spray administration, and this may be augmented by using special head positions.[70–72] Most existing studies that examined the efficacy of topical steroids used nasal spray application and should be interpreted with consideration to the method of administration. We recognize that the use of nasal steroids carries some controversy. However, we believe that the relative safety and low cost of topical steroids as well as the relative efficacy of using this modality in CRS carry greater weight than the low-risk profile of topical steroid use.[73] Of note, in a recent systematic review by Hura *et al.*,[74] topical or local steroid therapy was offered as an option with a balance of risk versus benefit.

There were several limitations of this work that must be acknowledged. Many patients with PVOD will recover a sense of smell and taste without intervention. Before the emergence of COVID-19, spontaneous recovery was found in 36–67% of patients over 1–3.5 years, with modifying factors of age, severity of smell loss, and duration of symptoms before treatment.[1–3] Analysis of early findings suggest that the incidence of spontaneous recovery may be even higher among patients who are mildly symptomatic and recovering from COVID-19.[6,75] Although these are welcome findings, the relatively high LOE of the interventions studied for PVOD with randomized designs and appropriate placebo groups minimizes this concern.

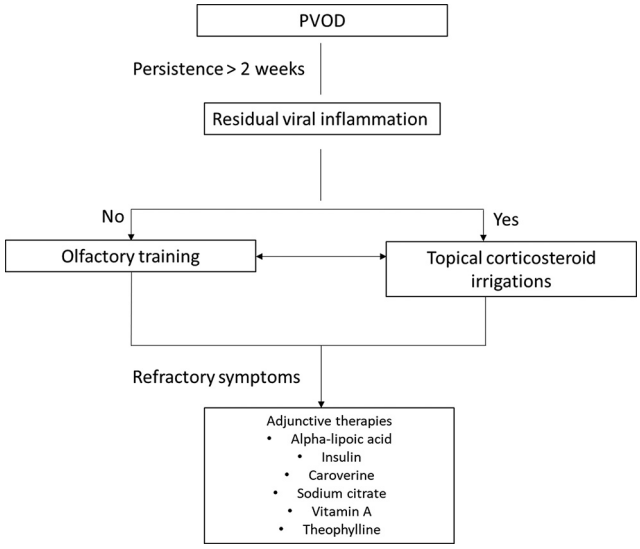

Figure 2. *Treatment algorithm.*

Although spontaneous recovery may occur, the available evidence supports initiating treatment for PVOD if OD persists beyond 2 weeks of URTI resolution.[68] Analysis of our data similarly highlighted OT as an important therapeutic adjunct. In one recent meta-analysis, there was a threefold greater odds of achieving a minimal clinically important change score in TDI in patients with OT relative to controls.[76] Our group's treatment algorithm adds to a recent body of literature that collates the available evidence[74,76] and is summarized in Fig. 2.

CONCLUSION

The results of this study provide an evidence-based approach for the treatment of this distressing condition. OT is recommended as a first-line therapy for the treatment of PVOD, with topical corticosteroids, sodium citrate, oral vitamin A, and TCA considered as optional therapies for appropriately selected patients. Although results of the studies to date suggest these therapies are likely to hasten resolution of PVOD above the rate of spontaneous recovery, additional research is needed to substantiate these interventions.

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